Atty's Docket:Kreisler 1089-KGB

CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, Applicants request that this be considered a petition therefore. Please charge the required fee to Deposit Account No. 14-1263.

ADDITIONAL FEES

Please charge any further insufficiency of fees, or credit any excess to Deposit Account No. 14-1263.

REMARKS

Claims 14- 26 are pending the application.

Formal Objections

A corrected substitute specification or replacement pages with follow shortly.

The claims have been amended to correct the spelling of cytokine, and other minor errors.

Enablement

Examiner finds that the claimed methods are not enabled by the specification. Specifically, that the claims must be limited to peptides of 9 or 15 amino acids. Respectfully, Applicants disagree for the following reasons. Apparently, Examiner is improperly trying to limit the claims to exemplified embodiments.

It is respectfully suggested that Examiner's remarks on pages 5 to 7 seem more relevant toward claims directed to the stimulatory peptides themselves; or perhaps compositions comprising the peptides.

Respectfully, Examiner's assumptions about predictability are not on target. The claimed method is a screening method -- it is contemplated by persons in the art that many, if not most peptides, may not be provide the desired degree of stimulation. However,persons in the art would expect this. It should also be

remembered that lack of stimulation also provides useful information in advancing this field of research.

Examiner claims that no one would no how to begin to choose amino acids of 8-30 amino acids. Respectfully, this is irrelevant. First, it should be made clear that at the point in a research project where peptides are being tested, it is because the entire protein or larger fragments thereof have already provided the stimulatory response. If this were not the case, there would be no reason to screen the peptides.

Put another way, the general approach in the art in identifying antigenic/stimulatory peptides is to go from longer to shorter pepides. The choice of the peptides will depend on the proteins/peptides of interest to persons in the art. Thus, Examiner's statement that "*there is no guidance in the specification as how one would begin to choose at least 8-30 amino acids*," is misguided because it fails to recognize that persons in the art who practice the claimed method automatically bring their own subject matter, expertise, reagents, probes, etc. Therefore, persons of ordinary skill would clearly be able to determine what peptides are of interest to them, and proceed accordingly.

Examiner states that the scope of the claims is not commensurate with the disclosure due to the large number of inoperative peptides; the inoperativeness being based on the alleged unpredictability of how changes in the peptide's sequence will affect its activity.

In response, it is reiterated that *any* screening method is expressly set up to deal with *the expected large numbers of negative results*, i.e., inoperative species, non-stimulating peptides, etc. This is the inherent nature of screening assays and, of the claimed method as well.

Examiner then asserts that recombinant techniques are known, but that it is not routine to screen for multiple substitutions. Respectfully, this is not applicable for the following reasons:

1. There is no recombinant proteins being made.
2. Even if there were recombinant proteins being made, it is indeed routine to remove, or add entire segments or domains of a protein by site specific mutagenesis.
3. The peptides disclosed on page 14 of the specification all differ by *at least two amino acids* -- *thus, the specification does in fact explicitly enable the practice of multiple substitutions*.

Therefore, Examiner's conclusion that considerations of protein structure place the claims "well outside the realm of routine experimentation" is not accurate. It would appear that Examiner has inadvertently conflated two similar but distinct kinds of claims: a method for screening the peptides in contrast to claims directed to the peptides.

In sum, the methodology described on pages 13-16, along with the figures, provide clearly enough guidance to perform the assay. Thus, the claims are enabled.

Examiner is reminded that the statements of fact in the specification must be accepted as true in the absence of reasonable doubts supported by sound technical reasoning or evidence. *In re Marzocchi et al.*, 169 USPQ 367, 369 (CCPA 1971). Respectfully, Examiner's concerns with regard to the predictability of protein function with changes in structure are, in this instance, only speculative, and do not satisfy the rule in *Marzocchi*.

Therefore, withdrawal of the rejection for alleged lack of enablement should be withdrawn.

Indefiniteness

Claim 14 has been amended to correct the antecedent issue in step b.

Claim 14 has been amended by adding the full name corresponding to MHC.

The Examiner asserts that it is not clear in 14(f) what are metes and bounds of *sufficiently long* and/or *short*, are concerned.

These terms functionally define the lengths of period for incubating the peptides with cells. More specifically, the terms refer to an incubation sufficiently long to stimulate one or more T-cell proliferation responses, BUT, short enough that the cells do not have the opportunity to divide in the presence of the peptide. In essence, the term functionally describes the window of time suitable for contacting the cells with peptides. Functional claim limitations are perfectly acceptable in format:

"A functional limitation is an attempt to define something by what it does, rather than by what it is (e.g., as evidenced by its specific structure or specific ingredients). There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971)." See MPEP § 2175.

It is respectfully requested that this rejection be withdrawn.

Anticipation by Woitas

Applicants respectfully disagree that Woitas anticipates the claimed method.

Paragraph (f) in claim 14 functionally delineates a window of time during which the incubation of T-cells with peptides is performed. This window of time is sufficient for the peptides to be taken up by the T-cells, but too short for there to be appreciable cell proliferation. In other words, a key part of Applicants' conception is an assay that reflects detecting the scope of distinctly proliferating stimulated cells.

Woitas' method leaves the peptides and cells together for 40 hours; see page 1013, col. 2, *Cells and Culture*. During such a long incubation, one could not discern whether a population of similarly stained cells were detected from one original cell or

a plurality of original cells, or a number of proliferated daughter cells derived from an original parent cell.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131.

Accordingly, it is respectfully requested that the anticipation rejection be withdrawn.

In addition, Woitas does not disclose the value of the foregoing issue; nor does he describe how to modify an assay to achieve it. Thus Woitas does not contain an enabling disclosure.

It is well established that a proper reference under 35 USC §§102 or 103 must be enabling in the sense of 35 USC §112, ¶1. Respectfully, Woitas not enabling to that extent. Pertinent is the following quote from *In re Le Grice,* 133 USPQ 365, 374 (CCPA 1962):

> "[T]he proper test of a description in a publication as a bar to a patent as the clause is used in section 102(b) requires a determination of whether one skilled in the art to which the invention pertains *could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put in possession of the invention* on which a patent is sought. [Emphasis added.]"

Woitas has not provided adequate guidance in obtaining an assay that inherently provides the kind of information obtainable in the claimed method. Woitas does not disclose the problem, let alone how to solve it. Thus, the claimed method cannot reasonably be held anticipated.

Applicants' respectfully request that the rejection be withdrawn.

Respectfully Submitted,

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AMENDMENT TO THE CLAIMS

1. to 13. (Canceled)

14. (Currently amended) A method for the identification of T-cell stimulating protein fragments comprising the following steps:

a) establishing the amino acid sequence of an antigen which is a protein or a peptide;

b) subdividing the ~~detected~~ amino acid sequence of said antigen into protein fragments;

c) synthesizing at least one protein fragment having a length of from 8 to 30 amino acids, or cleaving the amino acid sequence of said antigen into at least one protein fragment having a length of from 8 to 30 amino acids, wherein said protein fragment is a subsequence of the established amino acid sequence of said antigen;

d) incubating a suspension containing T cells with the protein fragment or fragments in different experimental runs;

e) identifying of

(I) at least one T cell ~~cytokin~~cytokine which has been induced by the protein fragment or fragments and synthesized in the T cells, wherein the T

cell ~~cytokin~~cytokine or ~~cytokin~~cytokinecytokinees remain within the cell or are bound to the cell membrane; and/or

(ii) at least one activation marker expressed or expression-enhanced due to the T cell stimulation by the protein fragment or fragments which has been induced or expression-enhanced by the protein fragment or fragments and which is expressed in the T cells, wherein said activation marker can be present within the cell or expressed on the cellular surface;

wherein said T cell ~~cytokin~~cytokine or ~~cytokin~~cytokines or activation markers are identified by flow cytometry; and

f) assigning the experimental runs in which T cells have been stimulated and such stimulation has been recognized by the identification of one or more T cell ~~cytokin~~cytokines and/or one or more activation markers, to the amino acid sequence or sequences of said protein fragments which had been incubated with the T cells;

characterized in that the incubation time is sufficiently long so that the protein fragment or fragments are sufficiently taken up by the major histocompatibility antigen (MHC) molecules present on the cellular surface, said taking up

being sufficient when an unambiguous identification of stimulated T cells is possible; and

the incubation time of the suspension containing T cells with the protein fragment or fragments is sufficiently short so that selection and proliferation accompanied by the specific elimination of particular T cells do not occur.

15. (Currently amended) The method for the identification of T-cell stimulating protein fragments according to claim 14, wherein said identification of at least one T cell ~~cytokin~~cytokine or activation marker is made on the individual cell level.

16. (Previously presented) The method for identification of T-cell stimulating protein fragments according to Claim 14, wherein said suspensions containing T cells contain cells which present the protein fragment essentially in a state bound to MHC class I or class II molecules.

17. (Previously presented) The method for the identification of T-cell stimulating protein fragments according to claim 14, wherein the protein fragment in the class I restricted presentation comprises from 9 to 11 amino acids, and the protein fragment in the

class II restricted presentation comprises at least 11 amino acids.

18. (Previously presented) The method for the identification of T-cell stimulating protein fragments according to claim 14, wherein said suspension containing T cells is a suspension of whole blood, peripheral white blood cells (PWBC), splenocytes, thymocytes, bone marrow, cerebrospinal fluid and/or lymph node cells.

19. (Previously presented) The method for identification of T-cell stimulating protein fragments according to claim 14, wherein said suspension containing T cells is derived from ~~the~~ patients to be subjected to therapy, from donors or from animals.

20. (Previously presented) The method for the identification of T-cell stimulating protein fragments according to claim 14, wherein the ~~antigens, i.e.,~~ protein or ~~peptides,~~ peptide antigens are derived from ~~polycellular~~multicellular multicellular eukaryotes, cells and/or tissues thereof, and cell cultures and/or tissues of donors or patients.

21. (Currently amended) The method for the identification of T-cell stimulating protein fragments according to claim 14, wherein the T cell ~~cytokin~~cytokines are of the types interferon-γ, tumor necrosis factor-α (TNF-α) or interleukin 2.

22. (Previously presented) A process for the preparation of a protein fragment/peptide which is T-cell stimulating and whose amino acid sequence or initial amino acid sequence was found by the method for the identification of T-cell stimulating protein fragments according to claim 14, wherein said protein fragment/peptide is prepared by the solid phase method, liquid phase method or by protein biosynthesis in a host.

23. (Previously presented) The process for the preparation of a protein fragment/peptide according to claim 22, wherein said protein fragment/peptide contains insertions, deletions or substitutions (modifications) wherein one, two, three or more amino acids have been exchanged, deleted or inserted, wherein said modified protein fragment/peptide has essentially the same function with respect to the stimulation of T cells as the non-modified protein fragment/peptide.

24. (Previously presented) The process for the preparation of a protein fragment/peptide according to claim 22, wherein said protein fragment/peptide contains at least one additional naturally occurring or not naturally occurring amino acid and/or protecting group at the N-terminal and/or C-terminal end (extended modification), wherein the extendedly modified protein fragment/peptide has essentially the same function with respect to the stimulation of T cells as the non-modified protein fragment/peptide.

25. Method of using of a protein fragment/peptide prepared by the process according to claim 22 for the preparation of a medicament for immune stimulation.

26. Method of using a protein fragment/peptide according to claim 25, wherein said immune stimulation is a vaccination or desensitization.